Mpox: Development of Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Kimberly Struble at 301-796-1500.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA is issuing this guidance to support sponsors in their development of drugs[1] for mpox. This guidance provides nonclinical, virology, and clinical considerations for mpox drug development programs, with a focus on recommendations to support initiation of clinical trials. Preventive vaccines are not addressed in this guidance. Development of preventative vaccines raise different and additional considerations, including those pertaining to subject selection, safety monitoring, and effectiveness evaluation. We encourage developers of preventative vaccines to contact the Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research.

Monkeypox virus is in the *Orthopoxvirus* genus of the *Poxviridae* family and is biologically similar to variola virus (the causative agent of smallpox). Although FDA has approved drugs for the treatment of smallpox under regulations commonly referred to as the Animal Rule,[2] this pathway is not applicable to drugs for mpox because researchers can design and implement clinical trials for mpox that are both ethical and feasible. The Animal Rule applies to the approval of drugs for serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances when it is not ethical to conduct definitive human efficacy studies and not feasible to conduct field trials to study the effectiveness of a drug after an accidental or hostile exposure.[3]

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic

[1] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[2] 21 CFR 314, subpart I (for drugs) and 21 CFR 601, subpart H (for biological products).

[3] See 21 CFR 314.600, 21 CFR 601.90, the guidance for industry *Product Development Under the Animal Rule* (October 2015), and the Animal Rule Information web page at https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-information. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. For further discussion, see Sherwat, A et al., 2022, "Tecovirimat and the Treatment of Monkeypox — Past, Present, and Future Considerations," N Engl J Med, 387:579–581.

and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. DRUG DEVELOPMENT PROGRAM CONSIDERATIONS

A. Regulatory Considerations

Sponsors developing drugs for mpox should consider the following:

- We recommend that sponsors seeking initial advice for mpox drug development submit a pre-investigational new drug application (pre-IND) meeting request. A pre-IND meeting allows for early discussion between the sponsor and FDA that can lead to more rapid review of a subsequent IND submission and facilitate faster clinical trial initiation.

- Sponsors should review the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017)[4] and Division of Antivirals (DAV) Pre-IND Letter of Instruction, located on the FDA website.[5] The pre-IND meeting package should also include the relevant content described in this guidance (see sections II. B, C, and D).

- Sponsors developing drugs for mpox have two options for submitting their pre-IND meeting requests:

  — **Option 1 (preferred method): Electronic Submissions Gateway (ESG)**[6] — ESG is an FDA-wide mechanism for accepting electronic IND, new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) regulatory submissions. The FDA ESG enables the secure submission of premarket and postmarket regulatory information for review.

  — **Option 2: NextGen Portal**[7] — The Center for Drug Evaluation and Research (CDER) NextGen Portal is a website providing a limited option for submission of pre-IND meeting requests and other submissions not subject to the electronic common technical document (eCTD) requirements.[8]

[4] The final, this guidance will represent FDA's current thinking on this topic. For most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

[5] See https://www.fda.gov/drugs/pre-ind-consultation-program/division-anti-viral-dav-pre-ind-letter-instruction.

[6] See FDA's ESG web page, available at https://www.fda.gov/industry/electronic-submissions-gateway.

[7] See CDER NextGen Portal web page, available at http://edm.fda.gov.

[8] For further information, see the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020).

B. Pharmacology/Toxicology Considerations

Sponsors developing drugs for mpox should consider the following:

- To support clinical trial initiation for small molecule drugs,[9] sponsors should provide the following data:
  - Data from good laboratory practice (GLP) compliant[10] general toxicology studies in two species (at least one nonrodent)[11]
  - An assessment of standard safety pharmacology parameters (e.g., cardiovascular, respiratory, and central nervous system assessments), which may be incorporated into general toxicology studies
  - The standard battery of genetic toxicology data[12]
- To support clinical trial initiation for biological products,[13] sponsors should provide the following data:
  - GLP-compliant general toxicology study or studies, when warranted
  - An assessment of standard safety pharmacology parameters (e.g., cardiovascular, respiratory, and central nervous system assessments) when warranted, which may be incorporated into general toxicology studies
  - Tissue cross-reactivity assay in human tissues, when indicated and technically feasible
- The active pharmaceutical ingredient should be the same between the toxicology studies and that proposed for use in clinical investigations when evaluating small molecule

[9] See the International Council for Harmonisation (ICH) guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

[10] See 21 CFR part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

[11] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[12] See the ICH guidance for industry *S2 (R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012).

[13] See the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012).

drugs. Similarly, the biological drug product used in the definitive pharmacology and toxicology studies and clinical investigations should be comparable.

- Additional nonclinical safety studies to support clinical trial initiation may be needed on a case-by-case basis. Nonclinical safety studies needed to support clinical development of small molecule drugs and biological products beyond clinical trial initiation are outside the scope of this guidance.

C. Virology Considerations

Sponsors developing drugs for mpox should consider the following:

- To support clinical trial initiation for small molecule drugs or biological products, sponsors should provide the following nonclinical virology information:

  — The hypothesized or determined mechanism of action of the drug, including a description of the target protein and information supporting the mechanism of action, such as binding data (e.g., KD values (quantitative measurement of antibody affinity)), enzymatic inhibition data (IC_{50} and IC_{90} values (50 percent and 90 percent inhibitory concentrations)), resistance characteristics, and structural analyses

  — Cell culture antiviral activity data (EC_{50} and EC_{90} values (50 percent and 90 percent effective concentrations) and concentration/response curves) against the current monkeypox virus outbreak strain/lineage

  — Data addressing the impact of serum proteins on antiviral activity in cell culture

  — Cytotoxicity (CC_{50} value (50 percent cytotoxic concentration)) assessments against cells used to characterize antiviral activity, and determination of a selectivity index (CC_{50} value/EC_{50} value)

  — Source and complete amino acid sequence of monoclonal antibodies, including a description of any Fc (fragment crystallizable) modifications and their expected pharmacologic effects

  — Competitive binding analyses for combinations of monoclonal antibodies

- Additional nonclinical virology studies that sponsors should conduct either before clinical trials or during clinical development to support NDA, or BLA submissions for small molecule drugs or biological products include the following:

  — Assessments of antiviral activity against geographically and temporally distinct monkeypox virus isolates

  — Mitochondrial toxicity and bone marrow precursor cell toxicity assessments for small molecule inhibitors potentially associated with this risk (e.g., nucleoside analogues)

148
149 — Identification of the epitope of monoclonal antibodies and characterization of the
150 impact of polymorphisms in the target protein contact and the adjacent (within 5
151 angstroms) amino acid residues on monoclonal antibody susceptibility
152
153 — Selection and characterization of virus that is resistant to the drug, including
154 genotypic and phenotypic analyses of polymorphisms occurring at or near resistance-
155 associated positions
156
157 — Assessments of combination antiviral activity if the drug is anticipated to be used in
158 combination with other antiviral treatments
159
160 • The need for studies in animal models of infection will be determined on a case-by-case
161 basis and should be discussed with FDA.
162
163 • Sponsors should address the possibility of drug and mpox vaccine interactions for drugs
164 that may interfere with vaccine effectiveness (e.g., monoclonal antibodies targeting a
165 critical vaccine antigen).
166
167 • Clinical trial protocols should include the following information related to planned
168 virology assessments. The specific types of assays and analysis plans may vary
169 depending on the objectives of the trial and mechanism of action of the drug.
170
171 — Description of diagnostic virology assays used for screening and enrollment,
172 including their regulatory status (e.g., FDA approved, FDA cleared, FDA authorized
173 (including under emergency use authorization provisions),[14] 510(k) exempt).
174
175 — Assay(s) and analysis plans to characterize the impact of drugs on viral DNA levels in
176 blood, lesion samples, and respiratory samples.
177
178 — Plans for detection in cell culture of infectious virus from clinical specimens.
179
180 — Plans to characterize the impact of drugs on antiviral immune responses.
181
182 — Genotypic and phenotypic resistance analysis plans, including analyses of baseline
183 viral polymorphisms and treatment-emergent resistance.
184
185 • FDA performs independent assessments of virologic and resistance data from clinical
186 trials. Sponsors should consult with FDA before submitting virology datasets to obtain
187 information on the most recent recommended formats. In the case of next-generation
188 sequence analysis, sponsors should refer to the technical specifications document

[14] See the guidance for laboratories, commercial manufacturers, and FDA staff *Policy for Monkeypox Tests to Address the Public Health Emergency* (September 2022).

Submitting Next Generation Sequencing Data to the Division of Antiviral Products (July 2019).[15]

- Sponsors should submit information on sample collection, assays performed, assay performance characteristics, and other validation approaches for virology assays. Using a specific procedure, method, or test system in an investigational protocol for a nonclinical laboratory study, or as a laboratory procedure supporting a clinical trial, does not constitute FDA endorsement of that procedure, method, or test system, or FDA approval for clinical laboratory use.

- Sponsors should refer to the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* (June 2006).

- Laboratory work with certain orthopoxviruses must comply with applicable regulations[16] and should incorporate relevant biosafety and biosecurity procedures as appropriate to the viruses studied. Sponsors should contact relevant government agencies, such as the Centers for Disease Control and Prevention and the National Institutes of Health, for more information regarding biosafety procedures.[17]

D. Clinical Considerations

Sponsors developing drugs for mpox should consider the following:

- Drugs should undergo sufficient early clinical development, including clinical evaluation for safety and tolerability, before sponsors submit proposals for evaluation in phase 2 or phase 3 clinical trials.

- To demonstrate substantial evidence of effectiveness,[18] development programs should include randomized controlled clinical trial data in participants with mpox. The primary endpoint for phase 2 or phase 3 clinical trials should be clinically meaningful and should demonstrate the clinical benefit with a favorable effect on a meaningful aspect of how a participant with mpox feels, functions, or survives. Sponsors should discuss appropriate endpoints for phase 2 and phase 3 clinical trials with the Agency.

[15] For the latest version of a technical specifications document, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[16] 42 CFR part 73. Additional information on the Federal Select Agent Program can be found at https://www.selectagents.gov.

[17] Information on biosafety can be found in the Centers for Disease Control and Prevention and National Institutes of Health's (NIH's) Biosafety in Microbiological and Biomedical Laboratories document available at https://www.cdc.gov/biosafety/publications/bmbl5/index.htm.

[18] See section 505(d) of the FD&C Act and 21 CFR 314.126. Also see the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- Current data indicate that mpox disproportionately affects racial and ethnic minorities, who should be represented in clinical trials.[19] Sponsors should ensure that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minorities to recruit a diverse study population.[20]

- Current data suggest that, in the United States, approximately 40 percent of mpox cases have occurred in individuals living with human immunodeficiency virus (HIV) infection.[21] Individuals living with HIV infection should not be excluded from clinical trials.

- It may be appropriate to incorporate proposals for adaptive designs in clinical trials evaluating drugs for mpox.[22] Such designs may give more flexibility and allow for prospectively planned modifications to the design based on its scientific context and accumulating data from participants in the trial. Sponsors should discuss these plans early with the Agency, especially when sponsors propose complex innovative designs, including complex adaptive designs.[23]

[19] Kava CM, Rohraff DM, Wallace B, et al., 2022, Epidemiologic Features of the Monkeypox Outbreak and the Public Health Response — United States, May 17–October 6, 2022, MMWR Morb Mortal Wkly Rep, 71(45):1449–1456.

[20] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[21] See the Centers for Disease Control and Prevention's Mpox and HIV web page available at https://www.cdc.gov/poxvirus/monkeypox/prevention/hiv.html.

[22] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019).

[23] See the guidance for industry *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products* (December 2020).